Analysis of Hungarian hospital antibacterial use from different aspects

Summary of Ph.D. thesis

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INTRODUCTION

The discovery of antimicrobial agents is considered to be one of the ten great public health achievements of the twentieth century. Initially, antibacterials were seen as truly miraculous drugs and considered the ‘‘panacea’’ of Medicine, but nowadays the evolution of drug-resistant organisms has greatly impaired their therapeutic efficacy. The development of antimicrobial resistance is a naturally occurring, multifactorial process that is further accelerated and amplified by misuse of antibacterials. The antimicrobial resistance crisis is heightened by the fact that only a limited number of new antibacterial drugs have been introduced into the market in the last three decades.

Antibiotics are one of the most commonly used medicines in hospitals and has substantial share from the hospitals' budget. As their inappropriate use has both medical (increased risk of side-effects, therapeutic failure), economic (financial burden) and public health consequences (selection of resistance) substantial efforts are needed to rationalise their use. Before designing any interventions aiming to optimise antibiotic use, data collection and evaluation is needed to identify problematic fields. The use of drugs could be evaluated at general population level and also at individual patient level. During my PhD work I intended to follow these steps.

AIMS

Drug utilization studies

- To analyse the changes in the amount and structure of antibacterial consumption in the hospital care sector in Hungary between 1996 and 2007
- To explore possible regional variations and investigate determinants of antibiotic consumption in hospital care in Hungary
- To show antibiotic related activities of Hungarian adult intensive care units (ICUs) and their parent institutes and analyse antibiotic use of Hungarian ICUs (preliminary study).

Pharmacokinetic study

- To analyse the pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with ventilator-associated pneumonia (VAP)
- To study the associations between pharmacokinetic and patient-related parameters
- To evaluate the theoretic pharmacokinetic/pharmacodynamic (PK/PD) appropriateness of different levofloxacin regimens.

METHODS

Drug utilization studies

All data on systemic antibacterial use (i.e. Anatomical Therapeutic Chemical (ATC) group J01) in hospitalized patients were expressed as Defined Daily Dose (DDD) per 100 patient-days. The 2008 version of the World Health Organization's ATC/DDD index were used for classifications and calculations. Hospital-specific antibiotics were defined, as previously proposed by the European Surveillance of Antibiotic Consumption (ESAC) project, as third- and fourth-generation cephalosporins, carbapenems, monobactams (note: they have never been marketed in Hungary), aminoglycosides, and glycopeptides.

National and regional level data were originated from the wholesale distribution database of the IMS PharmMIS Consulting Company, while antibiotic use in intensive care units were based on dispensing data of hospital pharmacy departments. Data on patient-days were based on financial statistics where the days of admission and discharge counted together as one patient-day. Trend analysis was used to investigate the trends in the national hospital antibiotic utilization through the study period. To investigate the determinants for regional differences in hospital antibiotic consumption, we applied a multiple linear regression method. Data on independent variables were extracted from the database of the Hungarian National Health Fund Administration, Hungarian Central Statistical Office and National Institute for Strategic Health Research. The association between hospital and ambulatory care antibiotic consumption in Hungarian regions was tested by the Pearson correlation test.

To assess the antibiotic related activities of Hungarian adult intensive care units (ICUs) and their parent institutes a retrospective questionnaire study was performed. After the validation process questionnaires were sent to the head of all adult Hungarian ICUs. Both the questionnaire development and the evaluation of results were based on the ARPAC (Antibiotic Resistance Prevention and Control) survey.

To explore differences and study relationships between antibiotic use and certain possible influencing factors (e.g. existence of written antibiotic guideline, ICU type, case-mix index) the analysis of variances (ANOVA) with Bonferonni post-hoc test or the Pearson correlation analysis was performed, as applicable. All statistical analyses were performed with the SPSS program package and P values < 0.05 were considered as statistically significant.

Pharmacokinetic study

A prospective, open-label study was performed between September 2003 and December 2005 in a 6-bed neurotrauma ICU. The protocol was previously approved by the local Ethics Committee. Patient inclusion criteria were the followings: (a) over 16 years of age; (b) suspected nosocomial VAP, defined as a Clinical Pulmonary Infection Score (CPIS) ≥ 6; (c) informed consent obtained from the closest relative, (d) normal renal function defined by an estimated creatinine clearance (CL_{CR}) > 50 mL/min, based on the Cockroft-Gault formula; (e) presence of intra-arterial and central venous lines in situ.

Levofloxacin (2×500 mg on the first day and 1×500 mg on consecutive days) was administered as a 1-hour intravenous infusion. Blood samples were collected at predetermined times, under steady-state conditions. The concentrations of free levofloxacin in the plasma were determined by high-pressure liquid chromatography (HPLC) after minor in-house modifications and validation of a previously developed method. Pharmacokinetic analysis was performed by the WinNonLin; statistical analysis by the SPSS program package. The possible association between pharmacokinetic and patient parameters was tested by multiple linear regression.

The pharmacokinetic/pharmacodynamic (PK/PD) appropriateness and the clinical/microbiological outcomes of levofloxacin therapy were assessed. Bacterial isolates were identified on species level using standard methods. Susceptibility to relevant antibiotics (including levofloxacin) prior to therapy was tested by the disc diffusion technique. The minimal inhibitory concentrations (MICs) of the different causative pathogens for levofloxacin were determined later, by the E-test method.

RESULTS

National data

The national standardized hospital antibiotic consumption remained relatively stable during the period 1996-2007 (mean ± standard deviation: 22.0 ± 1.7 DDD per 100 patient-days). In each year hospital-based antibiotic use accounted for 6.0-8.2 % of the total national consumption. In this section all values in the text in parenthesis refer to the two endpoints of the study: 1996 and 2007.

In 1996 the tetracyclines, from 1997 the penicillin plus beta-lactamase inhibitor combinations (J01CR) were the antibacterial group with the highest consumption and co-amoxiclav was the top one antibiotic agent (Figure 1). All other penicillins groups displayed a significant drop in use (Table 1). At the first part of the study the second-generation cephalosporins accounted for the bulk consumption of cephalosporins, while by 2007, the third-generation cephalosporins has played as important role as second-generation agents (Table 1). Cefuroxime was the most popular cephalosporin agent through the whole study period (Figure 1).

Carbapenems exhibited a significant increase in use (Table 1), by 2007 the use of meropenem and imipenem plus cilastatin were almost identical (0.14 vs. 0.16 DDD per 100 patient-days), while the new agent's, ertapenem role has remained marginal. As concerns glycopeptides, we observed a 3-fold increase in the use of vancomycin (0.05 vs. 0.15 DDD per 100 patient-days).

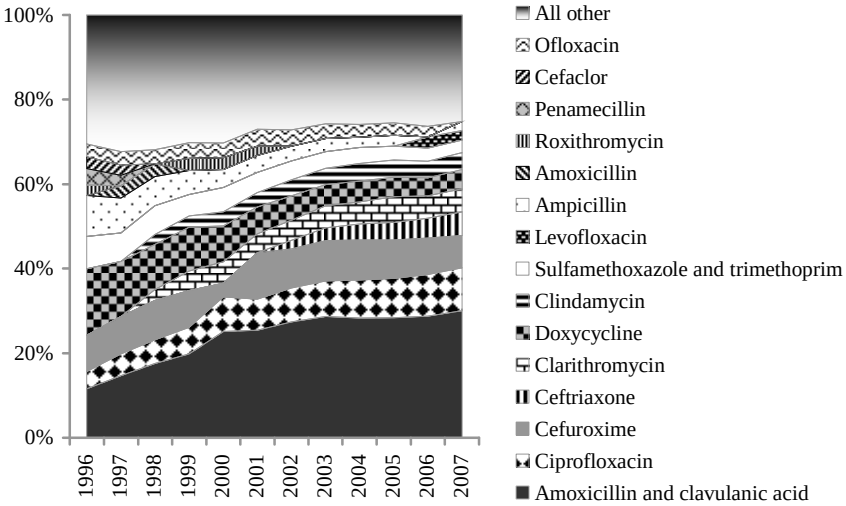
Table 1. National consumption of antibiotics in hospitals (DDD/ per 100 patient- days) in 1996 and 2007 (A) and results of the trend analysis for the 12 years of assessment (B)

	A			B	
Antibacterial group	1996	2007	% Change[c]	R[d]	P value
J01 Systemic antibacterials	24.14	23.28	-3.56	0.040	0.901
J01A Tetracyclines	3.80	1.06	-71.96	0.890	<0.001
J01CA Penicillins with extended spectrum	3.09	0.90	-70.74	0.878	<0.001
J01CE Beta-lactamase-sensitive penicillins	1.51	0.31	-79.82	0.886	<0.001
J01CF Beta-lactamase-resistant penicillins	0.03	0.06[a]	82.73	0.837	0.009
J01CR Penicillin combinations including beta-lactamase inhibitors	3.16	7.32	131.37	0.974	<0.001
J01DB First-generation cephalosporins	0.24	0.25	5.06	0.257	0.421
J01DC Second-generation cephalosporins	3.34	1.97	-41.02	0.609	0.036
J01DD Third-generation cephalosporins	1.02	1.98	95.37	0.928	<0.001
J01DE Fourth-generation cephalosporins	0.03[b]	0.04	36.10	0.510	0.161
J01DH Carbapenems	0.07	0.31	343.45	0.962	<0.001
J01E Sulfonamides and trimethoprim	1.98	0.70	-64.63	0.929	<0.001
J01FA Macrolides	1.30	1.68	28.96	0.363	0.246
J01FF Lincosamides	0.43	0.93	118.47	0.973	<0.001
J01G Aminoglycoside antibacterials	1.51	0.72	-52.05	0.837	0.001
J01M Quinolones	2.32	4.17	79.91	0.961	<0.001
J01XA Glycopeptide antibacterials	0.05	0.19	250.77	0.932	<0.001
J01XD Imidazole derivatives	0.30	0.44	47.47	0.209	0.515
Parenteral antibiotics	6.39	7.35	15.02	0.452	0.140
Hospital specific antibiotics[e]	2.65	3.25	22.64	0.574	0.051

a: data from 2003 (products were withdrawn from the market in the second half of 2003) , **b**: data from 1999 (products are available from 1999); **c:** percentage change as a percentage of the start value (1996); **d**: correlation coefficient; **e**: third- and fourth-generation cephalosporins, carbapenems, (monobactams), aminoglycosides, and glycopeptides.

The hospital usage of the sulfonamides and tetracyclines fell to one third of the original value, while the consumption of aminoglycosides was halved. The fluoroquinolones gained an extended usage in the hospital care, its most prominent representative, ciprofloxacin consumption doubled (0.97 vs. 2.36 DDD per 100 patient-days). Ofloxacine also showed a considerable use and was among the top 10 antibacterials until 2006, when a respiratory fluoroquinolone, levofloxacin replaced it in the top-list (Figure 1). During the study period, the national hospital use of antibacterials became less colourful: in 1996 the top-list leader doxycycline was responsible for 15.7% of total hospital antibacterial use, while in 2007 the co-amoxiclav shared 30.1 %.

Figure 1. The relative share of the top 10 antibacterials from total hospital antibacterial use in Hungary, 1996-2007



Regional differences and their determinants

Despite the stable national standardized hospital antibacterial use, there were large variations depending on the region: in each year during the study period (1996-2007), the difference between the regions with the lowest and the highest total hospital antibiotic consumption (maximum/minimum ratio) was ranged between 1.8 and 2.6. Both at the start and end point of the study, all antibiotic classes showed a large interregional variation in their use with a maximum/minimum ratio above two (Table 2). These regional differences were also present when the use of different antibacterial classes, parenteral antibacterials or hospital-specific antibiotics was considered.

The pattern of use also differed considerable between the Hungarian regions: the most prominent group, the penicillins recorded a relative use between 25.1 % and 49.2 %, second-generation cephalosporins between 5.0% and 16.6%, tetracyclines between 2.0 % and 11.3 %, and fluoroquinolones between 13.9 % and 23.2 % in 2007.

The heterogeneity of antibiotic use also showed interregional differences: in 1996, the number of active agents in the DU90% segment ranged from 17 to 23; while in 2007 it ranged from 13 to 22. In the county (Heves) with 13 antibacterials in the DU90 segment in 2007 several antibacterial groups (e.g. first-generation cephalosporins, beta-lactamase sensitive penicillin, penicillins with extended spectrum) were not represented in the DU90 segment, hence their use were marginal.

Table 2. Hospital antibiotic consumption in DDD per 100 patient-days of Hungarian regions (in 1996 and 2007)

	1996				2007			
Antibacterial group	Mean± SD[a]	Min	Max	Ratio Max/Min	Mean ± SD[a]	Min	Max	Ratio Max/Min
J01 Systemic antibacterials	24.24±3.67	15.96	28.24	1.77	21.89±5.79	13.38	34.57	2.58
J01A Tetracyclines	3.88±0.99	2.27	6.31	2.78	1.04±0.64	0.34	3.13	9.12
J01CA Penicillins with extended spectrum	3.16±1.42	0.94	6.86	7.28	0.78±0.44	0.18	1.91	10.47
J01CE Beta-lactamase-sensitive penicillins	1.51±0.72	0.63	3.40	5.35	0.32±0.21	0.06	0.83	14.03
J01CF Beta-lactamase-resistant penicillins	0.03±0.03	<0.01	0.08	nc			[b]	
J01CR Penicillin combinations including beta-lactamase inhibitors	3.04±0.97	1.22	4.95	4.06	6.96±1.82	3.45	10.82	3.14
J01DB First-generation cephalosporins	0.28±0.16	0.03	0.59	22.88	0.21±0.14	<0.01	0.45	nc
J01DC Second-generation cephalosporins	3.43±1.17	1.60	6.54	4.10	1.99±1.03	0.63	4.60	7.34
J01DD Third-generation cephalosporins	1.01±0.48	0.39	2.23	5.78	1.88±0.76	0.69	3.83	5.58
J01DE Fourth-generation cephalosporins			[c]		0.04±0.03	<0.01	0.12	nc
J01DH Carbapenems	0.05±0.06	0.01	0.28	nc	0.23±0.15	0.04	0.59	14.29
J01E Sulphonamides and trimethoprim	2.05±0.51	1.25	2.97	2.37	0.63±0.23	0.31	1.15	3.65
J01FA Macrolides	1.28±0.35	0.77	2.22	2.89	1.45±0.64	0.52	2.93	5.58
J01FF Lincosamides	0.39±0.19	0.06	0.94	16.24	0.84±0.37	0.21	1.75	8.30
J01G Aminoglycoside antibacterials	1.6±0.49	0.79	2.87	3.61	0.64±0.29	0.16	1.29	8.03
J01M Quinolones	2.18±0.62	0.94	3.11	3.30	4.01±1.21	2.59	6.77	2.61
J01XA Glycopeptide antibacterials	0.04±0.03	0.01	0.14	nc	0.15±0.09	0.06	0.33	5.28
J01XD01Imidazole derivatives	0.30±0.13	0.06	0.54	9.62	0.45±0.2	0.15	0.88	5.74
Parenteral antibacterials	6.63±1.46	4.25	8.73	2.05	6.98±2.07	3.17	10.86	3.43
Hospital specific antibacterials[d]	2.70±0.78	1.60	4.20	2.63	2.93±1.05	0.96	4.96	5.15

a: standard deviation.**;** **b**: not marketed in 2007; **c:** not marketed in 1996.; **nc**: ratio not calculated because of extreme low minimum value (min≤0.01)

d: third- and fourth-generation cephalosporins, carbapenems, (monobactams), aminoglycosides, and glycopeptides

Two models were built in the multiple linear regression: in Model 1 the entered variable was the number of reported infections, while in Model 2 the number of reported infections and the case mix index (CMI) determined hospital antibiotic use at regional level. Model 1 and Model 2 accounted for 53 % and 61 % of the observed regional variations in hospital antibiotic consumption, respectively. Other variables were excluded from both models: number of beds per 10,000 inhabitants; number of patient days per one hospital physician; percentage of active patient-days, percentage of patient-days in surgical units; percentage of patient-days in intensive care or infectious disease units; average length of stay; percent admitted cases aged 65 years or older and number hospital admissions per 10,000 inhabitants.

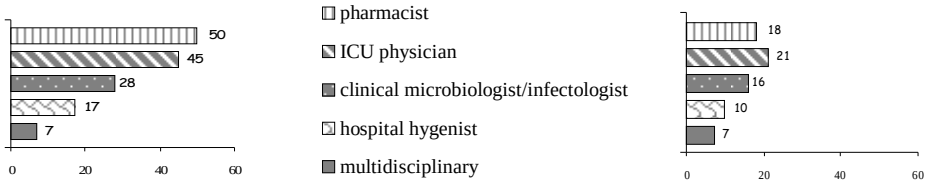
In the Pearson correlation test, interestingly, total antibiotic consumption in hospitals showed a positive and significant association with total antibiotic consumption in ambulatory care (R=0.71, p=0.002).

Antibiotic related activities in Hungarian adult intensive care units and their parent institutes

Responses were received from 60 Hungarian adult ICUs corresponding to a 62% response rate. Existence of drug therapy committee and antibiotic committee was reported in 58 (97%) and 23 (38%) hospitals, respectively. The involvements of different professions with special role in antibiotic use are summarized on Figure 2.

As concerns antibiotic therapy, multidisciplinary team – involvement of intensive care physician, clinical microbiologist/infectologist, hygienist and pharmacist were realized in 7-7 hospitals. In half of the hospitals (52%) the frequency of these committee meetings was twice a year or even less frequently.

Figure 2. Constitution of hospital committees



Constitution of drug therapy committees (N=58)

Constitution of antibiotic committees (N=23)

Written antibiotic policy and guideline for empiric antibiotic therapy was available in 27 (45%) ICUs. These guidelines were worked out in only 13 places (48%) by hospital committees. Pharmacists were only indirectly involved in these guideline developments, overall in 11 cases (41%). The four core information elements: first choice of drug, recommended dosage, alternative choice and length of

therapy were indicated in 27;22;20 and 11 guidelines, respectively. The four core information elements together were indicated in 9 guidelines.

Locally organized education on antibiotic use was performed in 35 ICUs (58%), education on both antibiotic use and consequences of resistance development was performed in 26 ICUs (43%) in the two years before completing the questionnaire. Pharmacists were involved in 3 cases (9%), pharmaceutical companies in 14 cases (40%) of these educational sessions. Continuous education on antibiotic use was realized in three ICUs (9%), while the efficacy of education sessions was surveyed in only 4 ICUs (11 %). Among the three most useful information sources the microbiology report (45 answers), national guidelines (37 answers) and the infectologist's advice (31 answers) were listed most often, and pharmacists were selected only once. Statistics on antibiotic use were performed in 33 units (55%). Financial aspects, frequency of antibiotic use, quality of antibiotic use and crude measure of quantitative antibiotic use (i.e. number of packages) were surveyed at 22, 20, 15 and 6 ICUs, respectively. Standardized antibiotic use expressed in DDD per 100 patient-days was calculated in only 5 ICUs (8%). Prescribers received personal feed-back on the results of the antibiotic use survey only in one ICU. As concerns the ward level activities of pharmacists, we found that they participated in daily rounds in none of the units. Most units never (25 answers, 42%) or maximum monthly (23 answers, 38%) ask the pharmacists about antibiotics. Improvement of antibiotic use is believed to be reached by education of doctors (45 answers, 75%). Only 5 units (8%) indicated that involvement of a pharmacist might help in rationalising antibiotic use in the future.

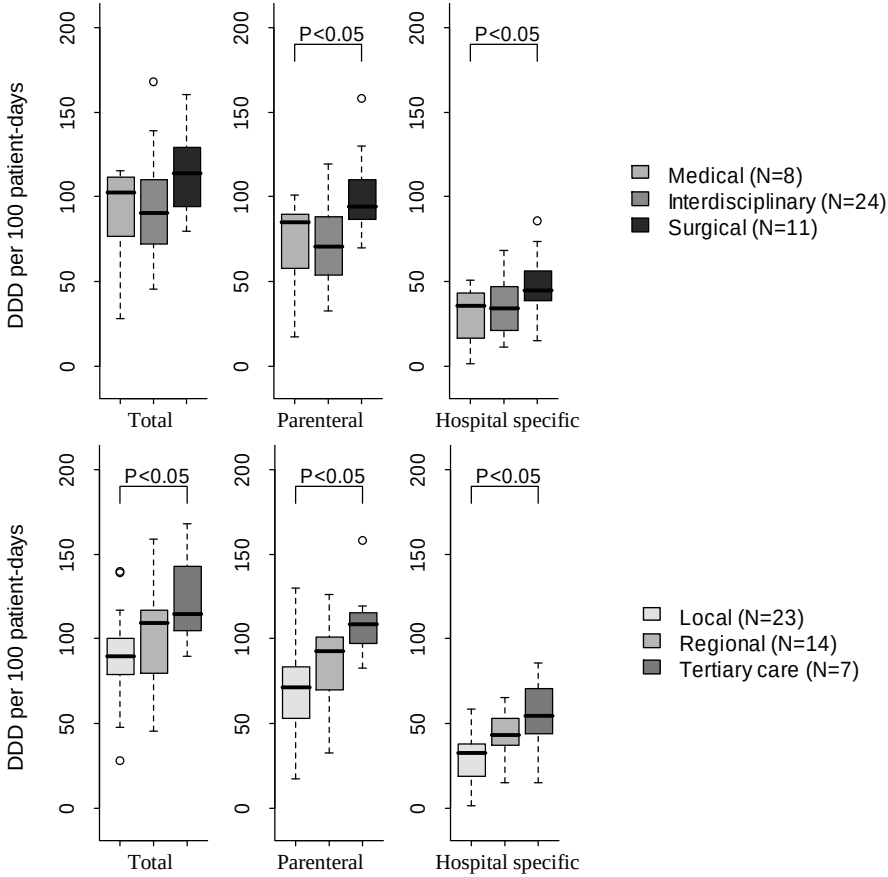
Antibiotic use in Hungarian adult intensive care units

Out of the 60 ICUs who participated in the questionnaire survey, 49 were able to provide crude antibiotic use data for 2006. During the validation process, 5 ICUs was excluded from the analysis.

Consumption of systemic antibacterials varied widely, ranging between 27.91 to 167.79 DDD per 100 patient-days. The proportional use of parenteral agents at Hungarian ICUs ranged between 46.15 to 98.30 % of total antibacterial use (in average: 81,03%). In surgical ICUs slightly higher total antibacterial use and significantly higher parenteral and hospital-specific antibiotic use were detected. Significant differences in total, parenteral and hospital-specific antibiotic use were also found between ICUs with different category (i.e. level of care) (Figure 3).

The mean of overall antibiotic use was highest for penicillins with beta-lactamase inhibitors, followed by quinolones and third generation cephalosporins (Table 3). Similar ranking were detected in interdisciplinary and surgical ICUs. In medical ICUs the consumption of quinolones out-ranged other classes of antibacterials (Table 3). Stratification by ICU type also showed differences in the use of second generation cephalosporins and glycopeptides which were used in higher quantities in surgical ICUs.

Figure 3. Box plot of antibiotic use stratified by ICU type and ICU category



In this pooled analysis, none of the elements of antibiotic policy (existence of written antibiotic guideline, antibiotic prescribing authority, restricted antibacterials, education on antibiotic use, frequency of infectologist consultation) showed to be accompanied by lower antibiotic use.

Association between antibiotic use in ICUs and the length of stay (R=0.104, P=0.502) or the case-mix index (R=0.023, P=0.857) also could not be detected in the correlation analysis.

Table 3. Antibiotic consumption in DDD per 100 patient-days in Hungarian ICUs, 2006

	All ICUs			Medical	Interdisciplinary	Surgical
Antibacterial group	Mean±SD	Min	Max	Mean		
J01 Systemic antibacterials	98.69 ±30.88	27.91	167.79	90.60	92.26	113.16
J01A Tetracyclines	0.77±1.91	0.00	8.75	0.94	0.90	0.45
J01CA Penicillins with extended spectrum	2.00±6.08	0.00	38.35	1.79	0.65	5.00
J01CE Beta-lactamase sensitive penicillins	0.59±1.39	0.00	6.65	0.13	0.71	0.70
J01CF Beta-lactamase resistant penicillins	0.35±1.16	0.00	5.44	0.00	0.11	1.17
J01CR Combinations of penicillins including beta-lactamase inhibitors	19.89±8.13	4.07	43.87	15.35	22.45	16.96
J01DB First-generation cephalosporins	0.31±0.63	0.00	2.32	0.00	0.24	0.55
J01DC Second-generation cephalosporins	5.33±7.98	0.00	39.16	3.57	3.16	11.30
J01DD Third-generation cephalosporins	15.19±9.44	0.00	40.22	10.24	15.88	15.45
J01DE Fourth-generation cephalosporins	1.28±1.86	0.00	7.46	1.03	0.90	1.86
J01DH Carbapenems	9.46±6.62	0.24	35.90	8.76	8.31	12.02
J01E Sulfonamides and trimethoprim	0.94±1.72	0.00	9.22	0.85	1.23	0.41
J01FA Macrolides	2.41±3.00	0.00	12.45	1.66	2.80	1.67
J01FF Lincosamides	2.57±2.19	0.00	9.58	3.22	2.22	2.39
J01G Aminoglycoside antibacterials	6.40±4.91	0.15	19.68	6.56	6.33	6.62
J01M Quinolone antibacterials	17.02±9.33	3.27	47.96	22.43	16.38	14.42
J01XA Glycopeptide antibacterials	5.57±10.32	0.00	64.42	3.63	3.13	12.35
J01XD Imidazole derivatives	8.49±8.38	0.00	44.16	10.45	6.73	9.61

SD: standard deviation

Pharmacokinetic study

Twelve of the 14 enrolled patients completed the study (Table 4). The primary diagnoses leading to ICU admission are listed in Table 5.All patients received levofloxacin as monotherapy, with an average length of treatment of 7 days. A high severity of illness (according to the Simplified Acute Physiology Score II), a low albumin level and a high estimated creatinine clearance (CL_{CR}) were general characteristics of the patient population (Table 4). The mean steady-state levofloxacin plasma concentration–time profile is shown in Figure 4, whilst overall pharmacokinetic variables are summarised in Table 4.

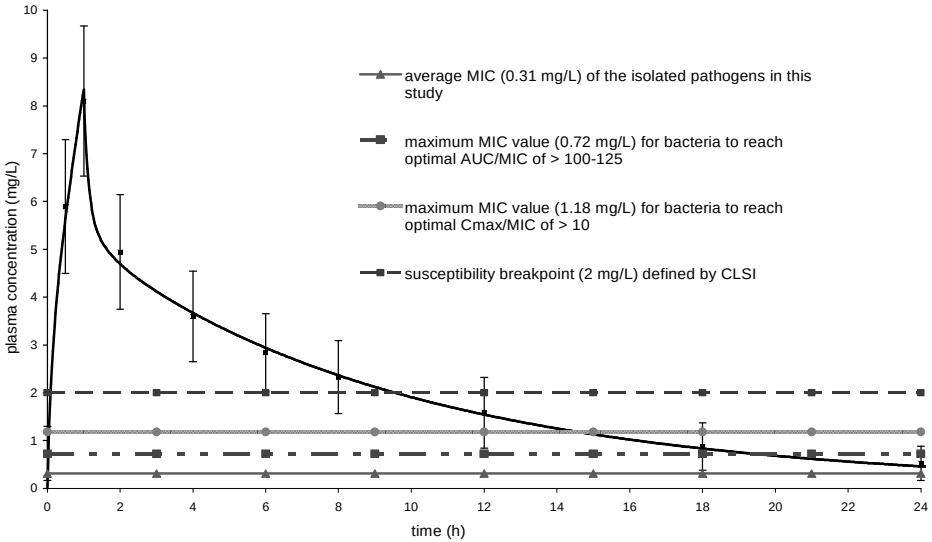
Of the 12 patients with ventilator-associated pneumonia (VAP), 11 had a microbiologically confirmed bacteriological aetiology. A total of 14 levofloxacin-sensitive microorganisms were isolated (Table 5). Methicillin-sensitive Staphylococcus aureus and Pseudomonas aeruginosa sensitive to most antipseudomonal drugs were the most frequent isolates.

Table 4. Patient characteristics and steady-state levofloxacin pharmacokinetic parameters following intravenous administration of a 500 mg/day maintenance dose to critically ill patients

Patient parameters (mean ± SD)		Pharmacokinetic parameters (mean ± SD)	
Males/Females	7/5	$fC_{max,ss}$ (mg/L)	8.13 ± 1.64
Age (years)	40.25 ± 22.01	$fC_{min,ss}$ (mg/L)	0.48 ± 0.33
Weight (kg)	72.33 ± 13.34	fV_d (L)	82.51 ± 18.93
SAPS II	40.42 ± 14.93	$T_{1/2\beta}$ (h)	6.23 ± 1.60
CL_{CR} (mL/min)	169.63 ± 55.94	CL (mL/min)	178.09 ± 57.98
Albumin (g/L)	29.08 ± 5.35	*f*AUC (mg·h/L)	49.63 ± 15.60

SD: standard deviation; **SAPS II**: Simplified Acute Physiology Score II, determined on the day of admission; **CL_{CR}**: estimated creatinine clearance based on the Cockcroft–Gault formula**;** ***f*$C_{max,ss}$**: maximum free plasma concentration at steady state; ***f*$C_{min,ss}$**: minimum free plasma concentration at steady-state, ***f*V_d**: volume of distribution; ***T*$_{1/2\beta}$**: elimination half-life; **CL**: total body levofloxacin clearance; ***f*AUC**: steady-state area under the free plasma concentration−time curve over 24 h.

Figure 4. Mean (±SD) steady-state plasma levofloxacin concentration − time profiles after multiple intravenous administration of 500 mg/day to patients with ventilator-associated pneumonia (n=12).



CLSI: Clinical and Laboratory Standards Institute; **AUC**: area under the concentration time curve over 24 h, **C_{max}**: maximum plasma concentration; **MIC**: minimum inhibitory concentration

At the end of levofloxacin therapy, eight patients were completely cured, three patients showed an improvement and treatment failed in one patient. Bacterial eradication of the aetiological agent was achieved in nine cases. However, in two cases merely a decrease in the number of CFU was observed. No superinfection was observed in any of the cases.

Table 5. Admission diagnosis, causative pathogens, individual pharmacokinetic and PK/PD parameters and outcome of levofloxacin therapy in critically ill patients with ventilator-associated pneumonia

Patient ID	Primary diagnoses	Aetiological agents	MIC (mg/L)	$fC_{max,ss}$ (mg/L)	$C_{max,ss}$ (mg/L)	fAUC (mg h/L)	AUC (mg h/L)	$C_{max,ss}$/MIC	AUC/MIC	Outcome	
										Clinical	Microbiological
01	SAH	N/A	N/A	7.68	11.13	41.26	59.80	N/A	N/A	Improved	N/A
02	T	*E. coli*	0.016	10.60	15.36	82.42	119.45	960.05	7465.67	Failure	Eradication
		E. cloacae	0.063					245.77	1911.21		Eradication
03	CSI	*K. pneumoniae*	0.125	5.94	8.61	34.87	50.53	68.90	404.26	Cure	Eradication
04	MT	*P. aeruginosa*	0.25	9.54	13.82	67.11	97.26	55.29	389.03	Cure	Eradication
05	MT	*S. aureus*	0.125	6.82	9.88	35.98	52.14	79.04	417.10	Improved	Eradication
		S. marcescens	0.125					79.04	417.10		Eradication
06	MT	*S. maltophilia*	0.25	6.31	9.15	28.28	40.98	36.60	163.93	Cure	Failure
07	BT	*P. mirabilis*	0.063	7.74	11.22	43.16	62.56	179.55	1000.88	Cure	Eradication
08	SAH	*S. aureus*	1	9.55	13.84	61.41	89.00	13.83	89.00	Improved	Failure
09	MT	*P. aeruginosa*	0.25	10.22	14.81	59.73	86.57	59.22	346.28	Cure	Eradication
10	MT	*S. aureus*	1	6.30	9.13	47.50	68.84	9.13	68.84	Cure	Eradication
		P. aeruginosa	0.125					73.06	550.75		Eradication
11	SAH	*E. coli*	0.032	7.62	11.04	41.12	59.59	345.11	1862.27	Cure	Eradication
12	MT	*Enterobacter* spp.	0.25	9.26	13.42	52.68	76.35	53.68	305.41	Cure	Eradication

MIC: minimum inhibitory concentration; $\boldsymbol{fC_{max,ss}}$: maximum free plasma concentration at steady-state; $\boldsymbol{C_{max,ss}}$: calculated maximum total plasma concentration at steady-state (i.e. after adjusting for 31% protein binding); ***f*AUC**: steady-state area under the free plasma concentration−time curve over 24 h; **AUC**: calculated steady-state area under the total plasma concentration−time curve over 24 h (i.e. after adjusting for 31% protein binding); **SAH**: subarachnoid haemorrhage; **N/A**: not available; **T**: trauma; **CSI**: cervical spine injury; **MT**: multiple trauma; **BT**: brain tumour.

The threshold AUC/MIC for a successful clinical/microbiological outcome of >100–125 was achieved in all but two cases. Optimal C_{max}/MIC (>10) was attained in 10 of the 11 available cases (Table 5).

The highest levofloxacin MIC of bacteria that fulfils the minimum AUC/MIC ratio (≥100) for the present dosage regimen and with the average pharmacokinetic parameters is 0.72 mg/L. To achieve the optimal C_{max}/MIC (≥10), the present dosing regimen would allow an MIC of 1.18 both for Gram-negative and Gram-positive pathogens (Figure 4). Table 6 shows the number of subjects (out of the 12 patients) with desired PK/PD target achievement at different dedicated MIC values with the 500 mg or 1000 mg daily levofloxacin regimen.

Table 6. Number of subjects of the 12 critically ill patients achieving desired pharmacokinetic/pharmacodynamic targets with 500 mg or 1000 mg daily levofloxacin, considering total drug exposure[a]

	Target PK/PD parameters	Study MIC[b]	Dedicated MIC values			
		0.31 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L[c]
500 mg/day levofloxacin	**C_{max}/MIC**	Number of patients achieving the indicated target C_{max}/MIC				
	10	12	12	12	8	0
	12	12	12	12	5	0
	AUC/MIC	Number of patients achieving the indicated target AUC/MIC				
	30	12	12	12	12	7
	50	12	12	12	11	1
	100	12	12	11	1	0
	125	12	12	7	0	0
	250	4	7	0	0	0
	Target PK/PD parameters	Study MIC[b]	Dedicated MIC values			
		0.31 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L[c]
1000 mg/day levofloxacin	**C_{max}/MIC**	Number of patients achieving the indicated target Cmax/MIC				
	10	12	12	12	12	8
	12	12	12	12	12	5
	AUC/MIC	Number of patients achieving the indicated target AUC/MIC				
	30	12	12	12	12	12
	50	12	12	12	12	11
	100	12	12	12	11	1
	125	12	12	12	7	0
	250	12	12	7	0	0

MIC: minimum inhibitory concentration; C_{max}: maximum total plasma drug concentration; **AUC**: area under the concentration–time curve; **a**: desired pharmacokinetic/pharmacodynamic target achievement, calculated from the observed individual pharmacokinetic parameters after correction for 31% protein binding (i.e. *f*AUC/0.69 = AUC); **b**: average MIC of the 14 pathogens isolated in this study; **c**: approved susceptibility breakpoint for levofloxacin.

We observed a weak positive association (R=0.73; P=0.005) between the levofloxacin clearance (CL) and the estimated creatinine clearance CL_{CR}. Further relationship between pharmacokinetic parameters and patient parameters were not revealed.

SUMMARY

My main findings are as follows:

- Total hospital antibiotic consumption in Hungary expressed as DDD per 100 patient-days remained relatively stable between 1996 and 2007. Some of the observed changes in the pattern of consumption are consistent with the national and international recommendations (decreased used of tetracyclines, sulfonamides, and aminoglycosides, increased use of respiratory fluoroquinolones), however the low first-generation cephalosporin and narrow spectrum penicillin (beta-lactamase sensitive and beta-lactamase resistant penicillins) use as well as the less heterogeneous antibacterial use require attention. In international comparison, the reason for substantial share of macrolide, lincosamide, fluoroquinolone, third-generation cephalosporin and penicillin plus beta-lactamase inhibitor consumption from total use should also be addressed in future pharmacoepidemiological studies.

- There were constantly large interregional differences in the Hungarian hospital antibacterial consumption. The pattern and heterogeneity of antibacterial use also differed considerable between Hungarian regions. The differences in total hospital antibacterial use were moderately explained by the number of reported infections and the case mix index (CMI), and surprisingly we observed a positive relationship between the regional hospital care and ambulatory care antibiotic consumption. All of these may suggest that other determinants that could not be explored in this dissertation (e.g. regional prescribing habits or marketing practices) may also contribute to regional differences. Therefore future studies should aim at collecting data for each individual hospital, as well as data on other possible determinants for hospital antibiotic consumption.

- Minimal requirements defined by the Antibiotic Resistance Prevention and Control (ARPAC) project have not been fulfilled in many aspects: multidisciplinary hospital committees were not realized, and the activity of hospital committees in the antibiotic guideline development was not satisfactory. The information content of empiric antibiotic guidelines was also deficient. Continuous education and calculation of standardized antibiotic use was rare. The role of pharmacist remained marginal in every field. All these findings suggest the need for appointment of a responsible, multidisciplinary antibiotic management team including a pharmacist.

- Consumption of systemic antibacterials varied widely (up to six fold) and the proportional use of oral agents also greatly differed at Hungarian adult ICUs. It was difficult to explain the quantitative differences; the only factor which showed significant association with total antibacterial use was the ICU category (i.e. level of care). However in many Hungarian ICUs this was the first time when antibacterial use was expressed in a standardized consumption unit. The striking differences in total antibiotic use and high use of oral agents in some ICUs – that could not be explained satisfactory in this study – may indicate room for improvement in some ICUs and require further analysis.

- Low dose (500 mg per day maintenance dose) intravenous levofloxacin therapy proved to be an effective regimen in this limited number of critically ill patients with VAP. The target PK/PD thresholds of clinical/microbiological efficacy (AUC/MIC ratio≥100; C_{max}/MIC ≥10) were exceeded in almost every case. The lack of relationship between C_{max}, AUC and patient parameters do not allow any prediction for these PK parameters. According to the measured pharmacokinetic parameters, the highest safe levofloxacin maintenance dose (1 g/day) would ensure optimal PK/PD levels up to an MIC of 1.5 mg/L, which is lower than the currently used MIC susceptibility breakpoints for levofloxacin (note: for most pathogens), therefore lowering of MIC susceptibility breakpoints for levofloxacin should be considered.

In conclusion, the continuous and close monitoring of antibacterial use at national, regional and local level should be considered as an important public-health priority to find problematic areas and trends which may require interventions. Also, the determination of optimal dosage in specific patient populations (i.e. ICU patients) could help in ensuring clinical/microbiological efficacy.

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